increases the number of chondrocyte population doublings in vitro.
Conclusions: Taken together these observations indicate that both aging and excessive articular surface contact stress may cause oxidative damage to chondrocytes, and that strategies that involve treating age related osteoarthritis in its earliest stages and joint injuries may be beneficial if they minimize deleterious mechanical stresses and prevent propagation of chondrocyte oxidative damage.

BIOMECHANICS AND MECHANOBIOLOGY OF OSTEOARTHRITIS: THE YEAR IN REVIEW

F. Guilak
Duke University Medical Center, Durham, NC

Purpose: Biomechanical factors play a critical role in the onset and progression of osteoarthritis, yet the mechanisms by which biomechanical and molecular factors interact to control cartilage physiology and pathology are not fully understood. Here we will review recent studies focusing on osteoarthritis and cartilage that have provided new insights on the role of biomechanics in OA.
Methods: In the past year, a number of exciting new studies have revealed new details on the role of biomechanical factors in the development, growth, remodeling, degeneration, and regeneration of joint tissues. Recent studies have focused at a variety of different scales and topics, including:
- Micro- and nano-mechanics of extracellular matrix molecules
- Cartilage cell and tissue mechanical properties
- Mechanobiology of cartilage and other joint tissues
- Interactions of biomechanics and inflammation in obesity
- The role of biomechanics in tissue engineering and cartilage regeneration

Results: These studies provide further evidence of the important role that biomechanical factors play in the function of the synovial joint, and in particular, how mechanical factors influence cell biology and vice versa.
Conclusions: An improved understanding of these mechanisms will hopefully lead to improved physical and pharmacologic therapies for osteoarthritis.

CLINICAL AND MOLECULAR GENETICS – THE YEAR IN REVIEW

J. Loughlin
University of Oxford, Oxford, United Kingdom

Purpose: The past year has been another highly productive one in the field of clinical and molecular genetics. New loci have been reported, and older loci have either been replicated or despatched from any further interest, in the objective style that makes genetic linkage and association analysis such powerful tools.
One of the most exciting new genes is GDF5, which codes for growth and differentiation factor 5 (also known as cartilage-derived morphogenetic protein 1). This signalling molecule, which is a member of the TGF-β superfamily, is active during joint formation and in mature tissues, implying both a design and maintain function. A common polymorphism in a regulatory element of the gene demonstrated a highly compelling association in Asian populations and this was soon replicated in large European cohorts. Subsequent meta-analysis on over 10,000 individuals has confirmed the global relevance of this gene to OA susceptibility whilst in-vitro and in-vivo functional studies have revealed that the associated polymorphism reduces the expression of GDF5 in chondrocytes. GDF5 joins the growing band of signalling or signalling-related genes that harbour polymorphisms that confer susceptibility for OA. This is an exciting development as these pathways are amenable to intervention.
Running alongside the new discoveries are the rumblings of the agnostic genome-wide association scans. There are highly progressed plans afoot for scans in North America, Europe and Asia on large case-control cohorts. Very soon the OA research community will be in the enviable position of understanding the molecular genetic architecture of OA with quite high precision. These are exciting times indeed.

CARTILAGE EXTRACELLULAR MATRIX IN HEALTH AND DISEASE

D. Heinegård
Lund University, Lund, Sweden

The cartilage extracellular matrix is progressively broken down and destroyed in joint disease leading to loss of tissue and joint function. There is accumulating evidence for degradation of cartilage extracellular matrix molecules at specific sites, following the original observations of one unique specific cleavage site by collagenases of triple helical collagen II and a total of five unique sites in aggrecan by aggrecanases. In these cases the normal and pathological turnover is accomplished by the same enzymes and the same sites are cleaved. New information on degradation of other matrix constituents indicates that there are processes involving enzymes that appear more unique to a pathological process and leading to unique cleavage sites. Antibodies raised to the new terminals produced in the substrate proteins offer opportunities to development of assays with a much higher specificity for the pathological process. Such assays can be used to depict sequence of events in the destruction process.
To understand the repair process that invariably is associated with breakdown, information needs to be gained about assembly of the constituent building blocks into larger structural assemblies such as the collagen fibrillar networks. There is accumulating information on the role of various cartilage matrix constituents in the regulation of the assembly of e.g. the collagen network. Such molecules include specific subsets of chondroitin sulfate, COMP and the leucine rich proteins, where there are examples of both accelerators and inhibitors. Dysregulation of any of these constituents is likely to hamper the process of tissue repair.
A key element is how cells react to events of the matrix. This is partly governed by mechanical load and by alterations in matrix constituents able to bind to receptors at the cell surface. New information is becoming available on interactions with a variety of cell surface receptors including integrins, cell surface proteoglycans and a number of others for specific molecules. Such interactions will be involved in modulating cellular activities relevant to the integrity of the matrix.
Degradation of matrix constituent will produce fragments of various macromolecules. Some of the fragment will be able to bind to and affect other players such as systems of factors and cells. One classical example is the fibronectin fragments that activate e.g. catabolic and inflammatory responses. It is now becoming apparent that also degradation of collagen will yield similarly active fragments. Inflammation is an almost invariable component of all joint diseases. New data are indicating that components in the cartilage may bind and regulate various players in the inflammatory system including macrophages and the complement system. This may yield activation of inflammation that in turn effect the cartilage to further breakdown in a vicious circle.

ADVANCES IN CLINICAL TRIAL DESIGN FOR OSTEOARTHRITIS

R.D. Altman
UCLA, Agua Dulce, CA

Instruments that measure change in osteoarthritis (OA) are not as sensitive as desired. In addition, the placebo response con-